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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,801	09/10/2003	Paolo Gatti	PC23575A	1817
28940	7590	05/24/2010		
PFIZER INC 10555 SCIENCE CENTER DRIVE SAN DIEGO, CA 92121			EXAMINER SCHLENTZ, NATHAN W	
			ART UNIT 1616	PAPER NUMBER
			NOTIFICATION DATE 05/24/2010	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/658,801	<b>Applicant(s)</b> GATTI, PAOLO	
	<b>Examiner</b> Nathan W. Schlientz	<b>Art Unit</b> 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 February 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 121-130 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 121-130 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Claims***

Claims 121-130 are pending in this application and are examined herein on the merits for patentability. No claim is allowed at this time.

### ***Withdrawn Rejections***

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

### ***Claim Objections***

Applicant is advised that should claims 121 and 123-126 be found allowable, claims 122 and 127-130 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 121 and 122 are made up of the exact same components in the exact same concentrations, and the components total 100% w/w. Therefore, neither claim can have an additional component making them exactly the same solid formulation. Thus, the claims are the same regardless of the

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transitional phrase (i.e., they are both solid formulations “consisting of” the components at their recited % w/w).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
1. Claims 121-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Tang et al. (WO 01/60814) and Shenoy et al. (WO 01/37820 A2).

### ***Determination of the scope and content of the prior art***

#### **(MPEP 2141.01)**

Tang et al. teach compositions comprising pyrrole substituted 2-indolinone compounds and their pharmaceutically acceptable salts (Abstract). Tang et al. teach that the pharmaceutically acceptable salt is prepared by reacting the free base of the

parent compound with inorganic acids, preferably hydrochloric acid or (L)-malic acid, such as the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (pg. 25, ln. 6-8). Tang et al. further teach on page 77 compositions comprising:

TABLE 2

Ingredient Name/Grade	Concentration in Granulation (% w/w)	Amount in 50 mg Capsule (mg)	Amount in 200 mg Capsule (mg)
Formulation Code	J-011248- AA	J-011248- AA-00	J-011248- AA-01
Active Compound NF	65.0	50.0	200.0
Mannitol NF	23.5	18.1	72.4
Croscarmellose sodium NF	6.0	4.6	18.4
Povidone K 30 NF	5.0	3.8	15.2
Magnesium stearate NF	0.5	0.38	1.52
Capsule, Swedish yellow NF		Size 3	Size 0

Tang et al. teach that pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, e.g., the modulation of PK activity or the treatment or prevention of a PK-related disorder. Determination of a therapeutically effective amount is well within the capability of those skilled in the art (pg. 80, ln. 29 to pg. 82, ln. 3). Tang et al. also teach cellular assay results, *in vivo* efficacy studies, efficacy in a model of disseminated disease, and biological activity of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (compound 80) (pg. 194 to pg. 208). Tang et al. teach that

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compound 80 crosses cellular membranes and penetrates into cells; has statistically significant inhibition of tumor growth; inhibited the growth of all the tumor types shown in Table 7; exhibited a pronounced inhibition of tumor cell proliferation; has profound anti-angiogenic and anti-tumor effects, even under conditions in which tumors do not regress; and a single oral dose resulted in high oral bioavailability. Tang et al. state that oral administration of compound 80 causes a direct effect on target activity in tumors *in vivo*, and dosing regimens may be determined by those with ordinary skill in the art without undue experimentation.

Shenoy et al. teach a formulation comprising 15-75 wt.% ionizable substituted indolinone, 5-95 wt.% binder, 4-10 wt.% disintegrant, and 1-1.5 wt.% lubricant (page 96, 2<sup>nd</sup> Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer"). Shenoy et al. further teach that 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide is a suitable ionizable substituted indolinone (page 39, compound 80; and pages 158-159, Example 80). Shenoy et al. also teach that the ionizable substituted indolinone contemplated for use are pharmaceutically acceptable salts which do not abrogate the biological activity and properties of the compound (page 60, lines 1-6), wherein the ionizable substituted indolinone is reacted with a molar equivalent of a base solution or an acid solution, such as malic acid (page 65, lines 1-4; page 76, lines 1-3).

Shenoy et al. also teach suitable pharmaceutically acceptable diluents include mannitol (page 73, lines 14-15); suitable pharmaceutically acceptable binders include polyvinylpyrrolidone (i.e. povidone) (page 73, lines 17-18); suitable pharmaceutically

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acceptable disintegrants include croscarmellose (page 73, lines 19-21); and suitable pharmaceutically acceptable lubricants include magnesium stearate (page 73, lines 26-27).

***Ascertainment of the difference between the prior art and the claims***

**(MPEP 2141.02)**

Tang et al. do not specifically teach the exact formulation comprising 40% w/w indolinone compounds, 47.5% w/w mannitol, 6% w/w croscarmellose sodium, 5% w/w povidone, and 1.5% w/w magnesium stearate, as instantly claimed. However, Shenoy et al. teach indolinone-containing compositions comprising 15-75% w/w indolinone, 5-95 wt.% binder, 4-10 wt.% disintegrant, and 1-1.5 wt.% lubricant (page 96, 2<sup>nd</sup> Table, “Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer”). Therefore, one of ordinary skill in the art could discover the workable ranges of Shenoy et al. through routine experimentation.

The examiner respectfully points out the following from MPEP 2144.05: “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S.

975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Tang et al. clearly teach solid formulations comprising the exact same components as instantly claimed. One of ordinary skill in the art would routinely be able to adjust the amounts of the components of the solid formulation within the limits of Shenoy et al. and still have a therapeutically effective solid formulation.

Tang et al. do not specifically teach capsules containing 25, 50 or 100 mg 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, as instantly claimed. However, Tang et al. teach capsules containing 50 mg or 200 mg active compound (Table 2). Also, Tang et al. teach that dosing regimens may be determined by those with ordinary skill in the art without undue experimentation. Tang et al. further teach that determination of a therapeutically effective amount is well within the capability of those skilled in the art (pg. 80, ln. 29 to pg. 82, ln. 3). Therefore, one of ordinary skill in the art would be able to determine the appropriate amount of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate per capsule in order to achieve a therapeutically effective dosage form.

### **Finding of *prima facie* obviousness**

#### **Rational and Motivation (MPEP 2142-43)**

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to determine the therapeutically effective amount of



indolinone compound, such as sunitinib L-malate, for incorporation in the compositions according to Tang et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### ***Response to Arguments***

Applicants argue on pages 5-8 of the Remarks filed 12 February 2010 that one must make numerous selections in Shenoy et al. in order to arrive at the instant invention, such as selecting the active agent from over 260 compounds, selecting the L-malate salt from a list of possible salts, select the solid formulation even though Shenoy et al. teach that the suspension has higher bioavailability, and selecting the specific component amounts in view of Shenoy et al. teaching extremely broad ranges. Applicants argue that the preferred compounds of Shenoy et al. have vastly different properties than the active being instantly claimed, and thus one of ordinary skill in the art would not be motivated to choose it as the active.

The examiner respectfully argues that Shenoy et al. teach that in a particularly preferred embodiment the indolinone compounds include numerous compounds that are structurally similar to sunitinib and have an amine as opposed to carboxylic acid group (pg. 14). Also, Tang et al. clearly teach sunitinib L-malate as a preferred compound for formulating solid dosage formulations that are very similar to Shenoy et

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al. Therefore, one of ordinary skill in the art would reasonably combine the teachings of Shenoy et al. with Tang et al. to arrive at the instant invention.

### ***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/

Primary Examiner, Art Unit 1616